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(FILE 'HOME' ENTERED AT 11:42:34 ON 23 JUN 2000)

FILE 'HCAPLUS' ENTERED AT 11:42:41 ON 23 JUN 2000

L1 250 S STELLA V?/AU
L2 31 S ZYGMUNT J?/AU
L3 1 S GEORG I?/AU
L4 8 S SAFADI M?/AU
L5 1 S L1 AND L2 AND L3 AND L4
L6 1 S L1 AND L2 AND L4
SELECT RN L5 1

FILE 'REGISTRY' ENTERED AT 11:43:17 ON 23 JUN 2000

L7 50 S E1-50

FILE 'HCAPLUS' ENTERED AT 11:43:26 ON 23 JUN 2000

L8 1 S L6 AND L7

Inventor Search

=> d bib abs hitstr

L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:117059 HCAPLUS
DN 132:171119
TI Water-soluble prodrugs of hindered alcohols or phenols
IN **Stella, Valentino J.; Zygmunt, Jan J.; Georg, Ingrid**
Gunda; **Safadi, Muhammed S.**
PA University of Kansas, USA
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	WO 2000008033	A1	20000217	WO 1999-US17779	19990806
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
PRAI	US 1998-131385		19980807		
OS	MARPAT 132:171119				
AB	Water-sol. phosphonooxymethyl esters of drugs contg. aliph. or arom. hindered OH groups are prepd. as prodrugs to improve the bioavailability of the drugs without use of surfactants which lead to severe side effects. Among the drugs thus rendered water sol. are camptothecin, propofol, cyclosporin A, etoposide, and .alpha.-tocopherol. Thus, propofol was converted via its O-(methylthio)methyl, O-chloromethyl, and O-phosphonooxymethyl dibenzyl ester derivs. to O-phosphonooxymethylpropofol. This compd. had a water soly. of .apprx.500 mg/mL, was nontoxic in rats, was converted to propofol by alk. phosphatase in vitro, and produced anesthesia in dogs in a similar manner to a com. propofol formulation (Diprivan).				
IT	16432-39-6DP , ethers RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses) (water-sol. prodrugs of hindered alcs. or phenols)				
RN	16432-39-6 HCAPLUS				
CN	Methanediol, mono(dihydrogen phosphate) (8CI, 9CI) (CA INDEX NAME)				

HO-CH₂-OPO₃H₂

IT **1406-18-4, Vitamin E 2078-54-8, Propofol**
Searched by John Dantzman 703-308-4488

7689-03-4, Camptothecin 7689-03-4D, Camptothecin,
analogs 33419-42-0, Etoposide 59865-13-3, Cyclosporin

A

RL: BAC (Biological activity or effector, except adverse); RCT
(Reactant);

THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(water-sol. prodrugs of hindered alcs. or phenols)

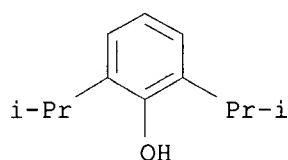
RN 1406-18-4 HCAPLUS

CN Vitamin E (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 2078-54-8 HCAPLUS

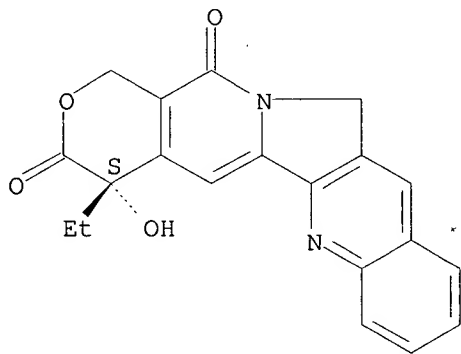
CN Phenol, 2,6-bis(1-methylethyl)- (9CI) (CA INDEX NAME)



RN 7689-03-4 HCAPLUS

CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione,
4-ethyl-4-hydroxy-, (4S)- (9CI) (CA INDEX NAME)

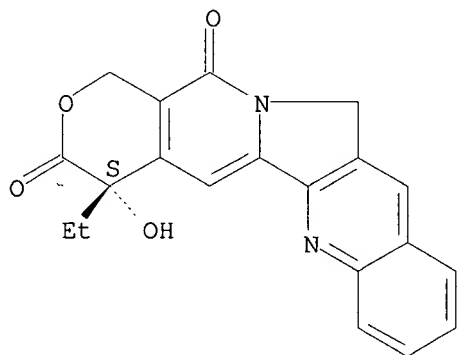
Absolute stereochemistry.



RN 7689-03-4 HCAPLUS

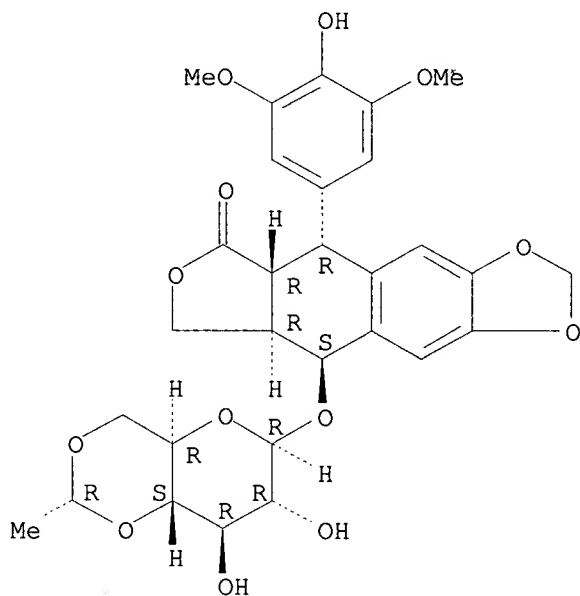
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione,
4-ethyl-4-hydroxy-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 33419-42-0 HCAPLUS
CN Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, 9-[[4,6-O-(1R)-ethylidene-.beta.-D-glucopyranosyl]oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-, (5R,5aR,8aR,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



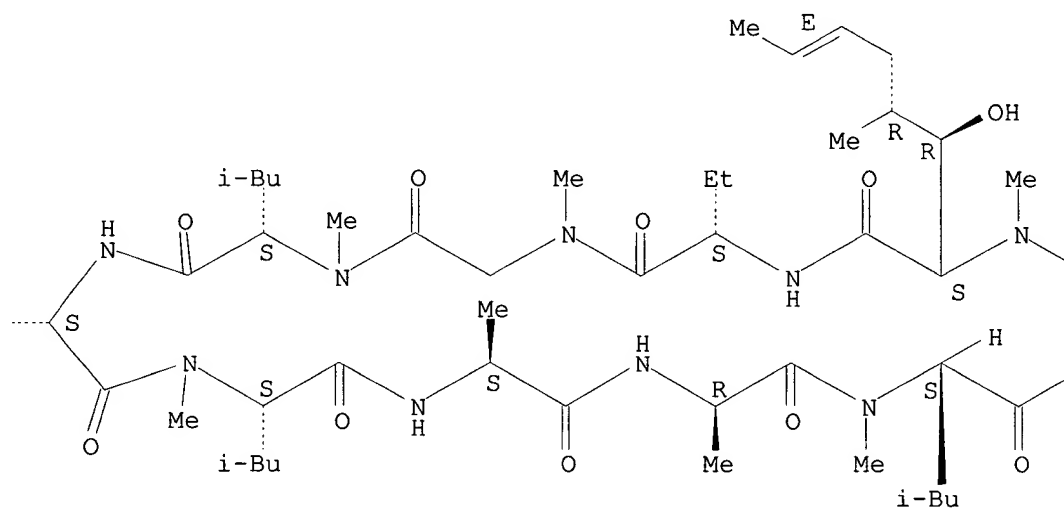
RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

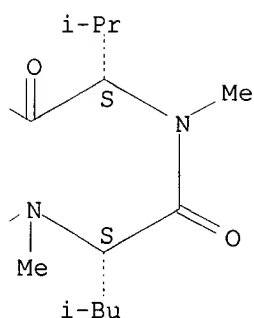
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PAGE 1-B



PAGE 1-C

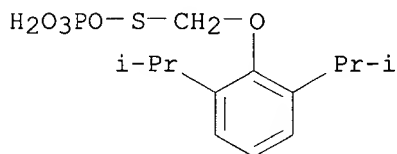


IT 258516-87-9P 258516-89-1P 258516-91-5P
 258516-93-7P 258516-95-9P 258516-97-1P
 258516-99-3P 258517-01-0P 258517-02-1P
 258517-03-2P 258517-04-3P 258517-05-4P
 258517-08-7P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (water-sol. prodrugs of hindered alcs. or phenols)

RN 258516-87-9 HCAPLUS

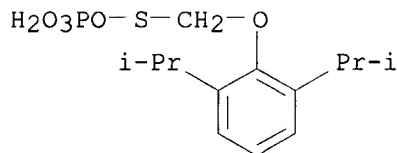
CN Phosphoro(thioperoxoic) acid, OS-[[2,6-bis(1-methylethyl)phenoxy]methyl] ester, disodium salt (9CI) (CA INDEX NAME)



● 2 Na

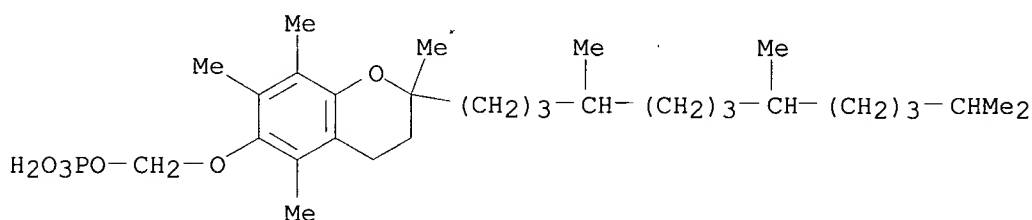
RN 258516-89-1 HCAPLUS

CN Phosphoro(thioperoxoic) acid, OS-[[2,6-bis(1-methylethyl)phenoxy]methyl] ester (9CI) (CA INDEX NAME)



RN 258516-91-5 HCAPLUS

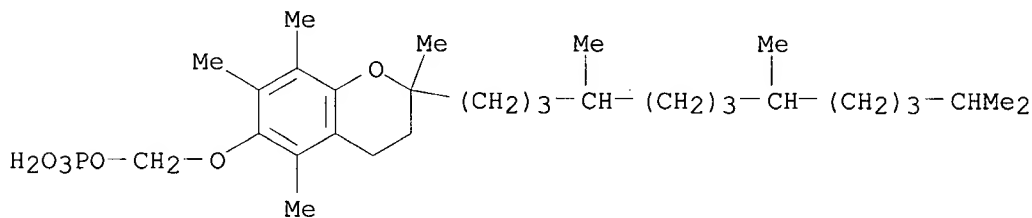
CN Methanol, [[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy]-, dihydrogen phosphate (9CI) (CA INDEX NAME)



RN 258516-93-7 HCAPLUS

CN Methanol, [[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy]-, dihydrogen phosphate, disodium salt (9CI)

(CA INDEX NAME)

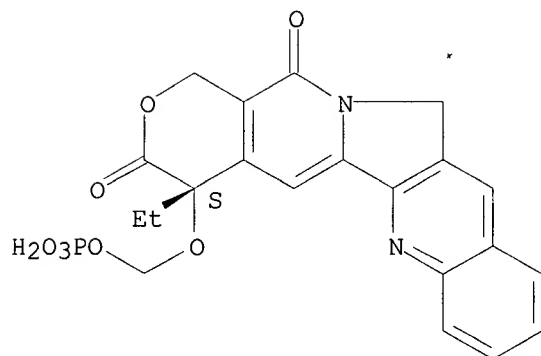


● 2 Na

RN 258516-95-9 HCAPLUS

CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-[(phosphonooxy)methoxy]-, (4S)- (9CI) (CA INDEX NAME)

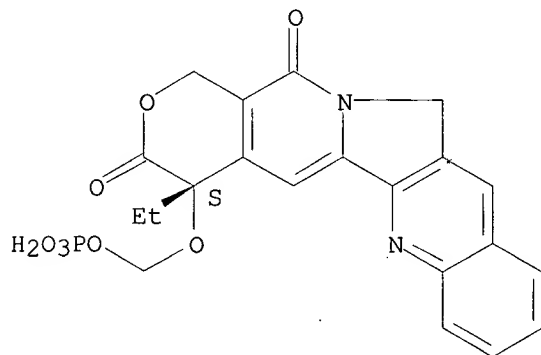
Absolute stereochemistry.



RN 258516-97-1 HCAPLUS

CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione,
4-ethyl-4-[(phosphonoxy)methoxy]-, disodium salt, (4S)- (9CI) (CA INDEX
NAME)

Absolute stereochemistry.

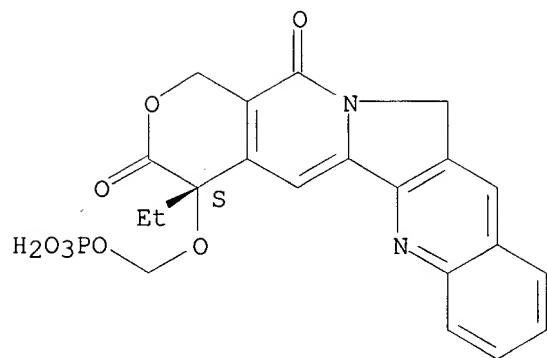


● 2 Na

RN 258516-99-3 HCAPLUS

CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione,
4-ethyl-4-[(phosphonoxy)methoxy]-, monosodium salt, (4S)- (9CI) (CA
INDEX NAME)

Absolute stereochemistry.



● Na

RN 258517-01-0 HCAPLUS

CN L-Lysine, compd. with (4S)-4-ethyl-4-[(phosphonoxy)methoxy]-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione (1:1)
(9CI)

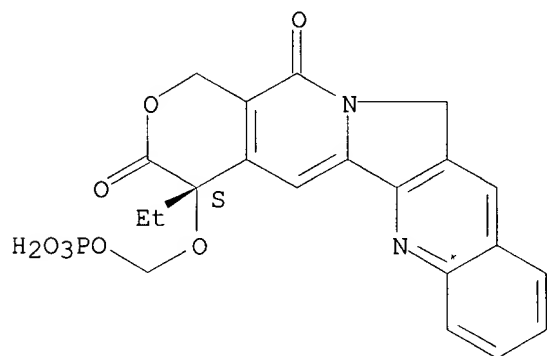
(CA INDEX NAME)

CM 1

CRN 258516-95-9

CMF C21 H19 N2 O8 P

Absolute stereochemistry.



CM 2

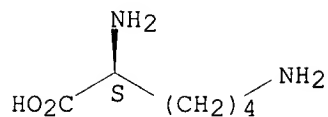
CRN 56-87-1

CMF C6 H14 N2 O2

CDES 5:L

Absolute stereochemistry.

Searched by John Dantzman 703-308-4488



RN 258517-02-1 HCAPLUS

CN L-Arginine, compd. with (4S)-4-ethyl-4-[(phosphonooxy)methoxy]-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione (1:1) (9CI)

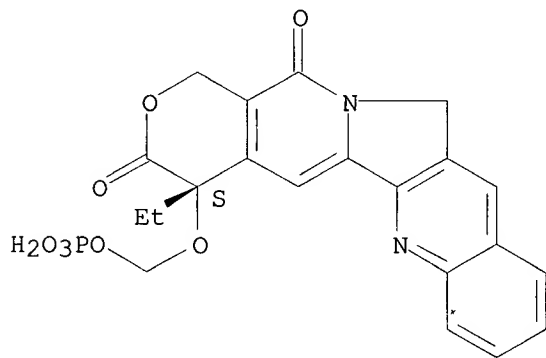
(CA INDEX NAME)

CM 1

CRN 258516-95-9

CMF C21 H19 N2 O8 P

Absolute stereochemistry.



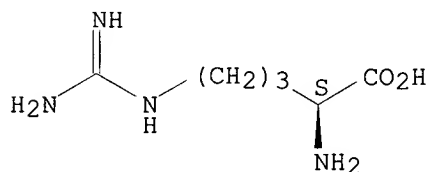
CM 2

CRN 74-79-3

CMF C6 H14 N4 O2

CDES 5:L

Absolute stereochemistry.



RN 258517-03-2 HCAPLUS

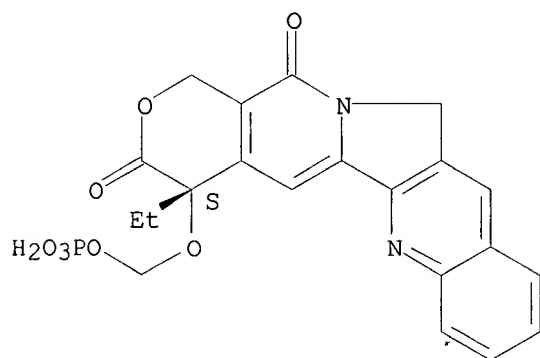
CN D-Glucitol, 1-deoxy-1-(methylamino)-, compd. with (4S)-4-ethyl-4-[(phosphonooxy)methoxy]-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione (1:1) (9CI) (CA INDEX NAME)

CM 1

Searched by John Dantzman 703-308-4488

CRN 258516-95-9
CMF C21 H19 N2 O8 P

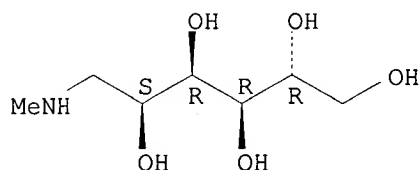
Absolute stereochemistry.



CM 2

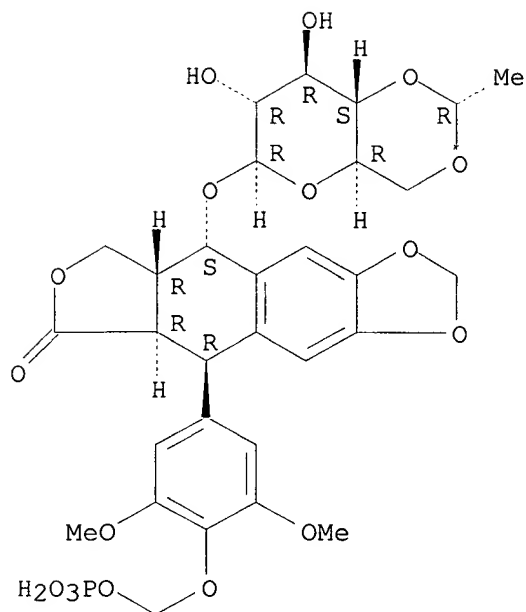
CRN 6284-40-8
CMF C7 H17 N O5
CDES *

Absolute stereochemistry.



RN 258517-04-3 HCAPLUS
CN Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, 5-[3,5-dimethoxy-4-
[(phosphonooxy)methoxy]phenyl]-9-[[4,6-O-(1R)-ethylidene-.beta.-D-
glucopyranosyl]oxy]-5,8,8a,9-tetrahydro-, (5R,5aR,8aR,9S)- (9CI) (CA
INDEX NAME)

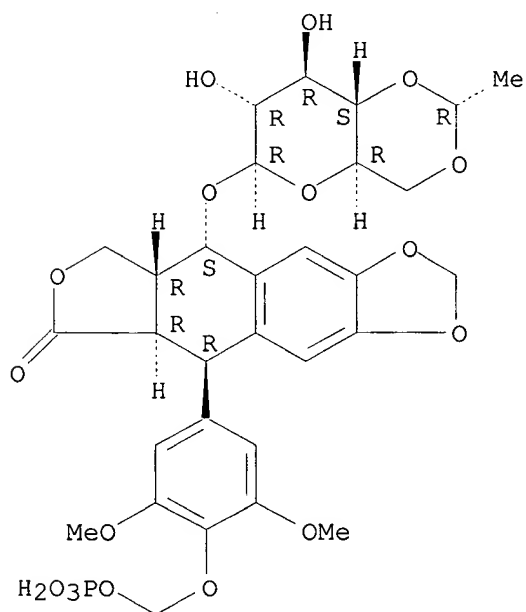
Absolute stereochemistry.



RN 258517-05-4 HCAPLUS

CN Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, 5-[3,5-dimethoxy-4-[(phosphonooxy)methoxy]phenyl]-9-[[4,6-O-(1R)-ethylidene-.beta.-D-glucopyranosyl]oxy]-5,8,8a,9-tetrahydro-, disodium salt, (5R,5aR,8aR,9S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 Na

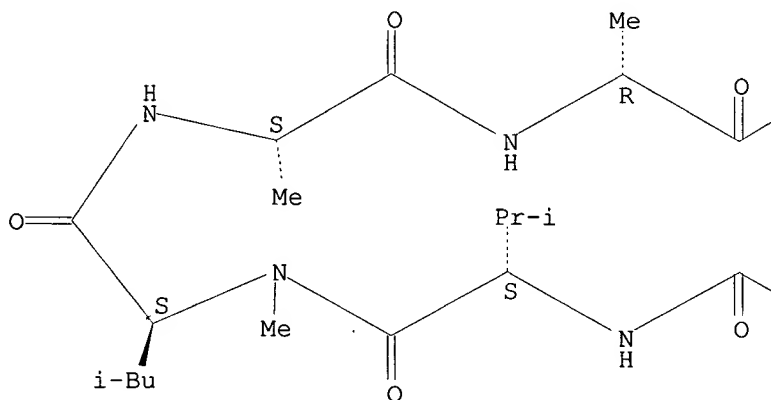
RN 258517-08-7 HCAPLUS

CN Cyclosporin A, 6-[(2S,3R,4R,6E)-4-methyl-2-(methylamino)-3-
[(phosphonoxy)methoxy]-6-octenoic acid]- (9CI) (CA INDEX NAME)

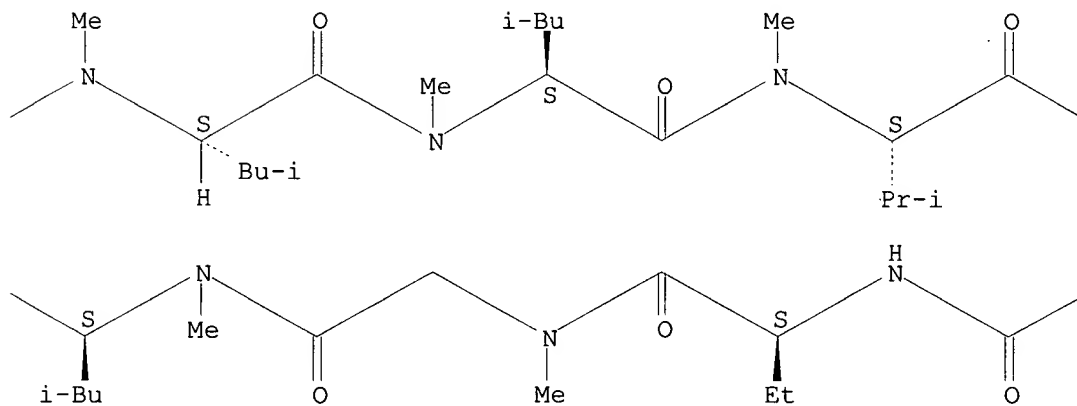
Absolute stereochemistry.

Double bond geometry as shown.

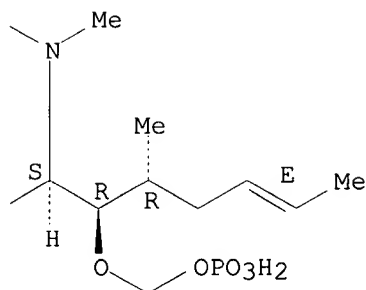
PAGE 1-A



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PAGE 1-C



IT 9001-78-9

RL: CAT (Catalyst use); USES (Uses)
(water-sol. prodrugs of hindered alcs. or phenols)

RN 9001-78-9 HCAPLUS

CN Phosphatase, alkaline (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 593-71-5, Chloriodomethane 1623-08-1, Dibenzyl
phosphate 2373-51-5, Chloromethyl methyl sulfide
10191-41-0 16836-95-6, Silver p-toluenesulfonate
50651-75-7, Silver dibenzyl phosphate

RL: RCT (Reactant)

(water-sol. prodrugs of hindered alcs. or phenols)

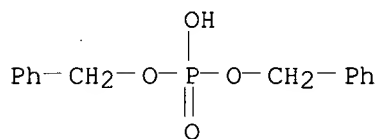
RN 593-71-5 HCAPLUS

CN Methane, chloriodo- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

Cl-CH₂-I

RN 1623-08-1 HCAPLUS

CN Phosphoric acid, bis(phenylmethyl) ester (9CI) (CA INDEX NAME)



RN 2373-51-5 HCAPLUS

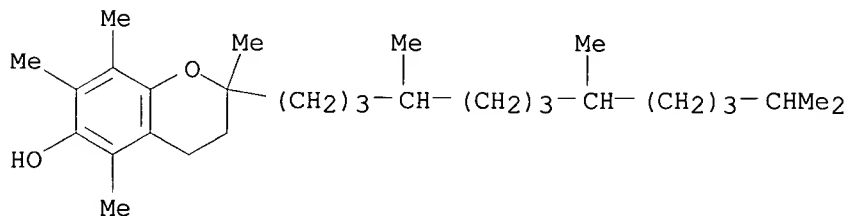
CN Methane, chloro(methylthio)- (9CI) (CA INDEX NAME)

Cl-CH₂-S-CH₃

RN 10191-41-0 HCAPLUS

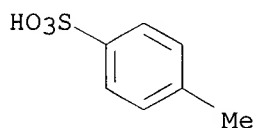
Searched by John Dantzman 703-308-4488

CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)- (9CI) (CA INDEX NAME)



RN 16836-95-6 HCAPLUS

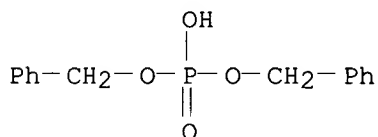
CN Benzenesulfonic acid, 4-methyl-, silver(1+) salt (9CI) (CA INDEX NAME)



● Ag(I)

RN 50651-75-7 HCAPLUS

CN Phosphoric acid, bis(phenylmethyl) ester, silver(1+) salt (9CI) (CA INDEX NAME)



● Ag(I)

IT 74418-05-6P 258516-17-5P 258516-21-1P
 258516-25-5P 258516-32-4P 258516-36-8P
 258516-40-4P 258516-44-8P 258516-48-2P
 258516-51-7P 258516-55-1P 258516-58-4P
 258516-61-9P 258516-64-2P 258516-67-5P
 258516-69-7P 258516-72-2P 258516-75-5P
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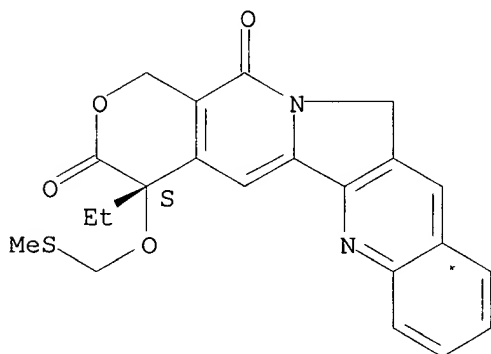
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
 (water-sol. prodrugs of hindered alcs. or phenols)

RN 74418-05-6 HCAPLUS

Searched by John Dantzman 703-308-4488

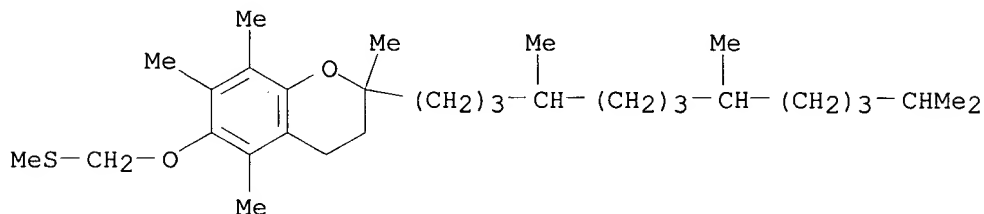
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione,
4-ethyl-4-[(methylthio)methoxy]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 258516-17-5 HCAPLUS

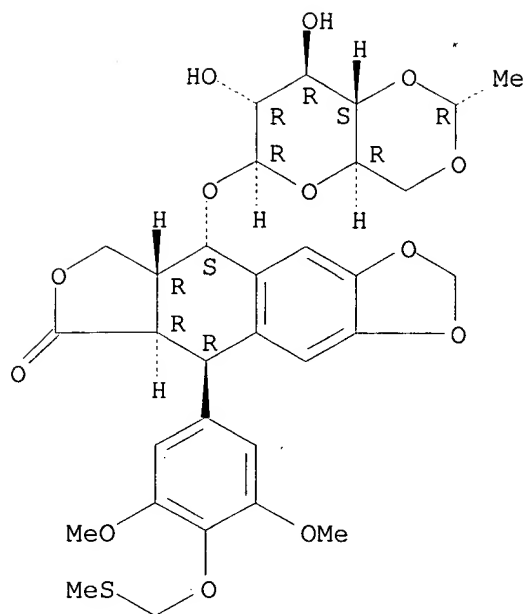
CN 2H-1-Benzopyran,
3,4-dihydro-2,5,7,8-tetramethyl-6-[(methylthio)methoxy]-2-
(4,8,12-trimethyltridecyl)- (9CI) (CA INDEX NAME)



RN 258516-21-1 HCAPLUS

CN Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, 5-[3,5-dimethoxy-4-
[(methylthio)methoxy]phenyl]-9-[[4,6-O-(1R)-ethylidene-.beta.-D-
glucopyranosyl]oxy]-5,8,8a,9-tetrahydro-, (5R,5aR,8aR,9S)- (9CI) (CA
INDEX NAME)

Absolute stereochemistry.

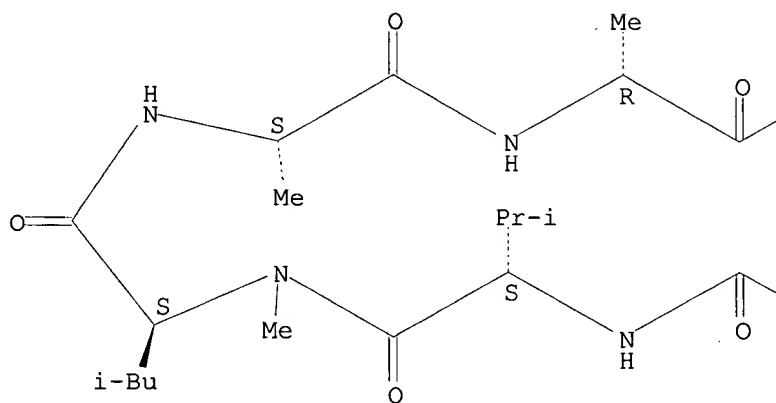


RN 258516-25-5 HCAPLUS

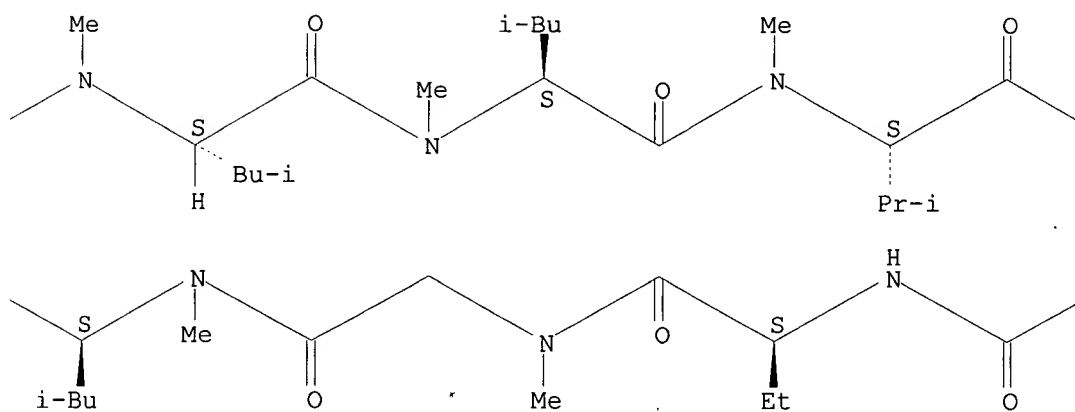
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-4-methyl-2-(methylamino)-3-[(methylthio)methoxy]-6-octenoic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

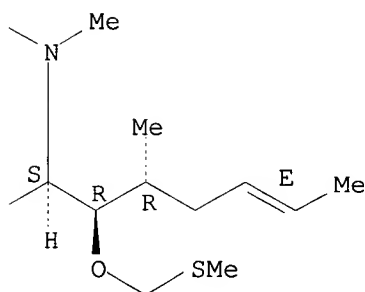
PAGE 1-A



PAGE 1-B

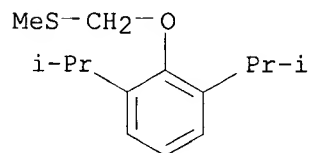


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RN 258516-32-4 HCAPLUS

CN Benzene, 1,3-bis(1-methylethyl)-2-[(methylthio)methoxy]- (9CI) (CA INDEX NAME)



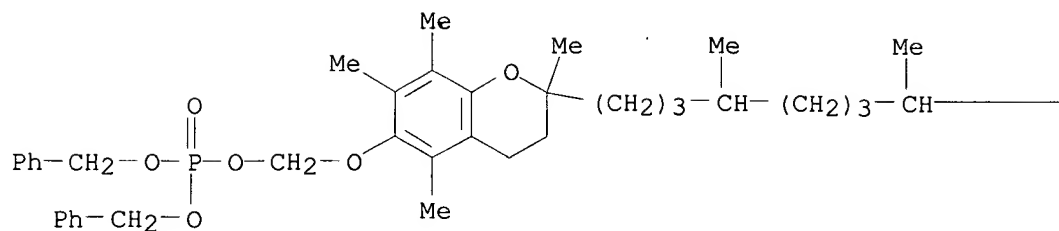
RN 258516-36-8 HCAPLUS

CN Phosphoric acid, [[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy]methyl bis(phenylmethyl) ester

(9CI) (CA INDEX NAME)

Searched by John Dantzman 703-308-4488

PAGE 1-A



PAGE 1-B

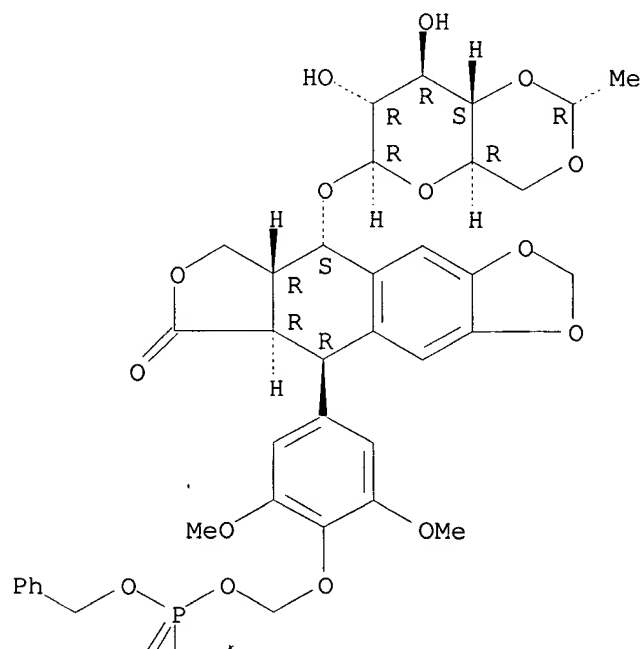
— (CH₂)₃—CHMe₂

RN 258516-40-4 HCAPLUS

CN Phosphoric acid, 4-[(5R,5aR,8aR,9S)-9-[[4,6-O-(1R)-ethylidene-.beta.-D-glucopyranosyl]oxy]-5,5a,6,8,8a,9-hexahydro-6-oxofuro[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-5-yl]-2,6-dimethoxyphenyl bis(phenylmethyl) ester (9CI) (CA INDEX NAME)

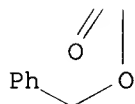
Absolute stereochemistry.

PAGE 1-A



Searched by John Dantzman 703-308-4488

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RN 258516-44-8 HCAPLUS

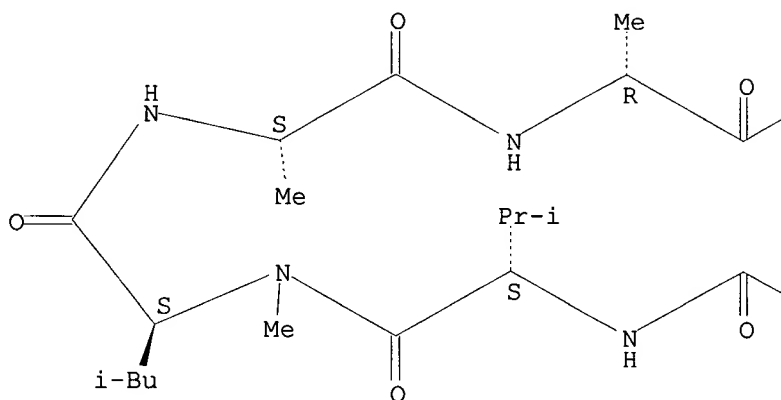
CN Cyclosporin A,

6-[[2S,3R,4R,6E]-3-[[[bis(phenylmethoxy)phosphinyl]oxy]methoxy]-4-methyl-2-(methylamino)-6-octenoic acid]- (9CI) (CA INDEX NAME)

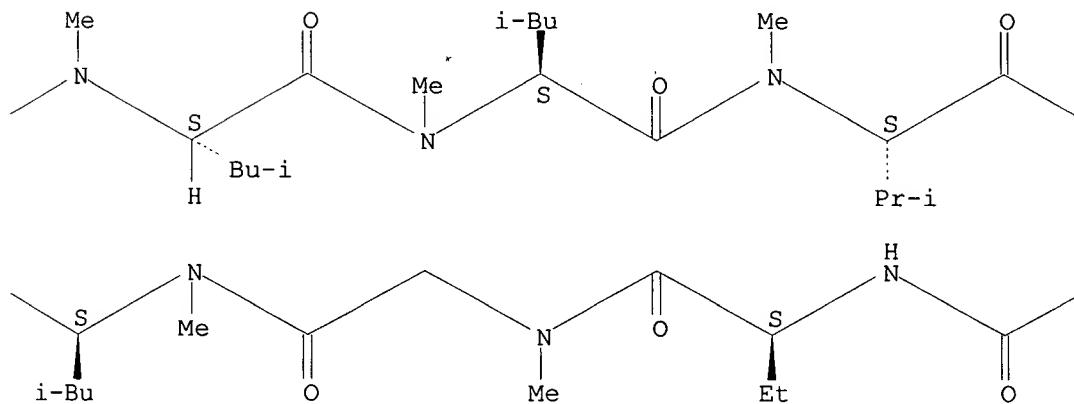
Absolute stereochemistry.

Double bond geometry as shown.

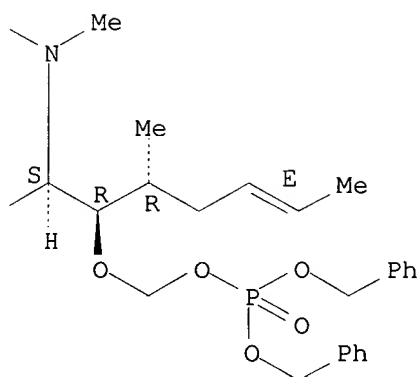
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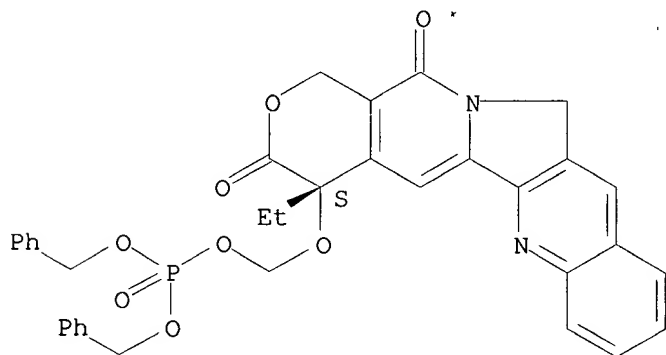
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RN 258516-48-2 HCAPLUS

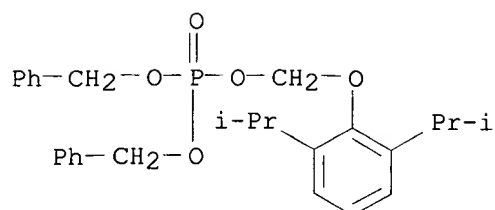
CN Phosphoric acid, [[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl]oxy]methyl bis(phenylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



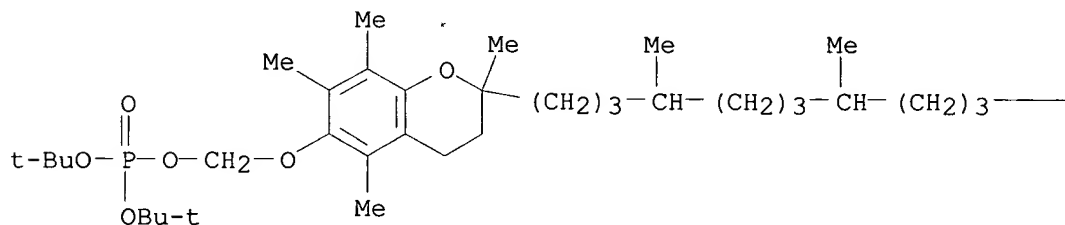
RN 258516-51-7 HCAPLUS

CN Phosphoric acid, [2,6-bis(1-methylethyl)phenoxy]methyl bis(phenylmethyl) ester (9CI) (CA INDEX NAME)



RN 258516-55-1 HCAPLUS
 CN Phosphoric acid, [[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy]methyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

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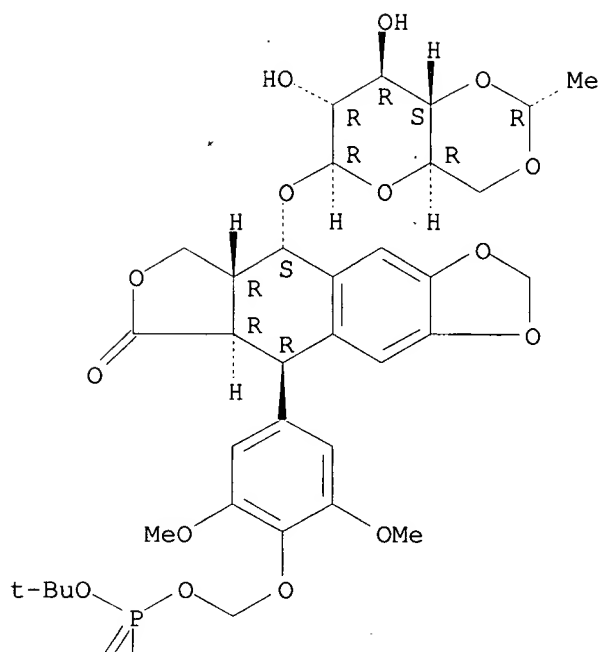
PAGE 1-B

— CHMe₂

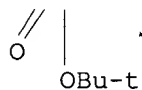
RN 258516-58-4 HCAPLUS
 CN Phosphoric acid, bis(1,1-dimethylethyl)
 4-[(5R,5aR,8aR,9S)-9-[[4,6-O-(1R)-ethylidene-.beta.-D-glucopyranosyl]oxy]-5,5a,6,8,8a,9-hexahydro-6-oxofuro[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-5-yl]-2,6-dimethoxyphenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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RN 258516-61-9 HCAPLUS

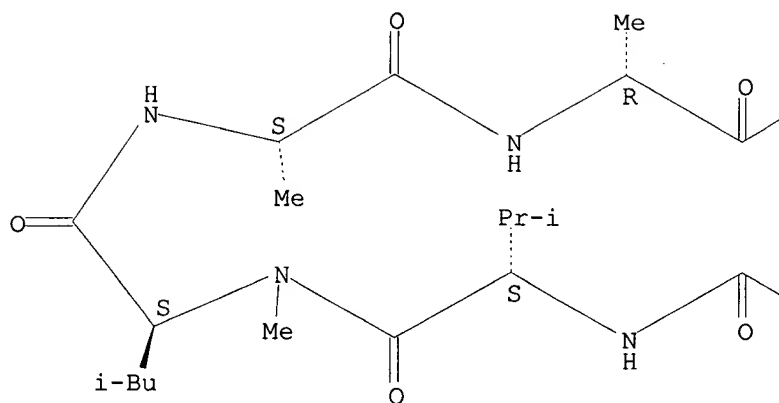
CN Cyclosporin A,

6-[(2S,3R,4R,6E)-3-[[[bis(1,1-dimethylethoxy)phosphinyloxy]
]methoxy]-4-methyl-2-(methylamino)-6-octenoic acid]- (9CI) (CA INDEX
 NAME)

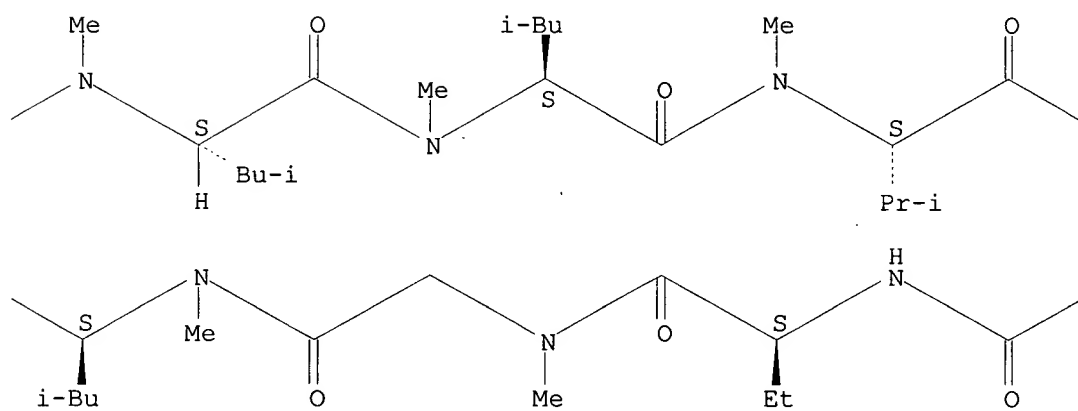
Absolute stereochemistry.

Double bond geometry as shown.

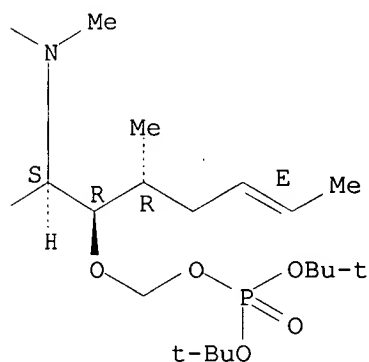
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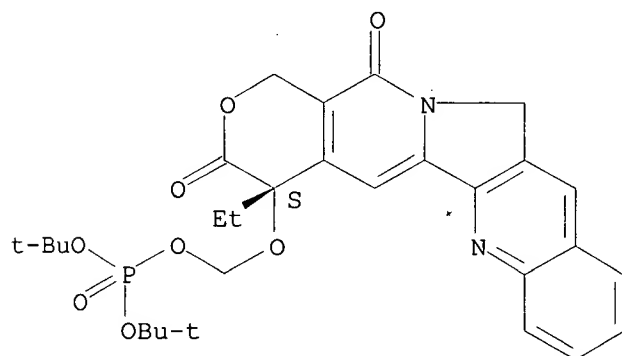
PAGE 1-C



RN 258516-64-2 HCAPLUS

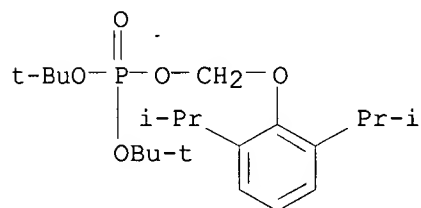
CN Phosphoric acid, bis(1,1-dimethylethyl) [[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl]oxy]methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



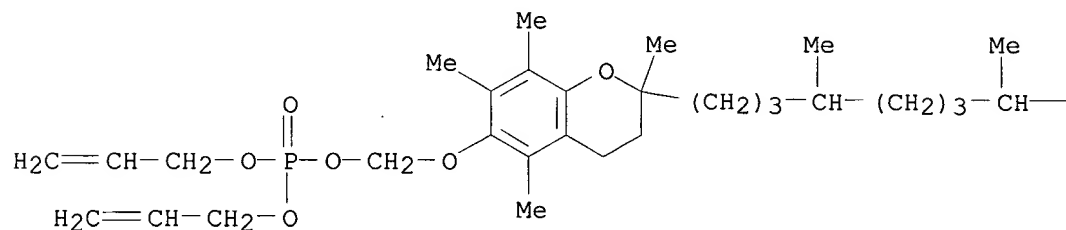
RN 258516-67-5 HCAPLUS

CN Phosphoric acid, [2,6-bis(1-methylethyl)phenoxy]methyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



RN 258516-69-7 HCAPLUS
CN Phosphoric acid, [[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy]methyl di-2-propenyl ester (9CI) (CA INDEX NAME)

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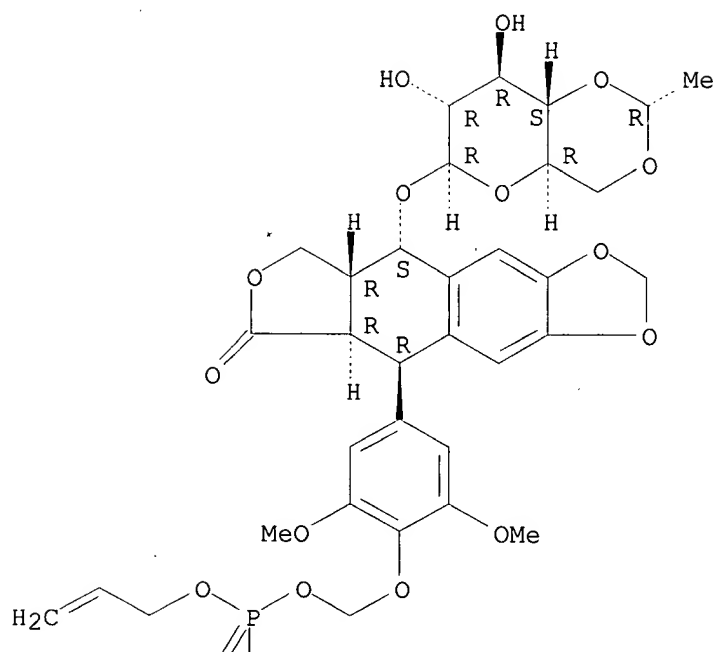
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— $(\text{CH}_2)_3\text{-CHMe}_2$

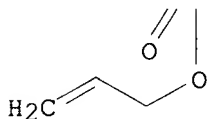
RN 258516-72-2 HCAPLUS
CN Phosphoric acid, 4-[(5R,5aR,8aR,9S)-9-[[4,6-O-(1R)-ethylidene-.beta.-D-glucopyranosyl]oxy]-5,5a,6,8,8a,9-hexahydro-6-oxofuro[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-5-yl]-2,6-dimethoxyphenyl di-2-propenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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RN 258516-75-5 HCAPLUS

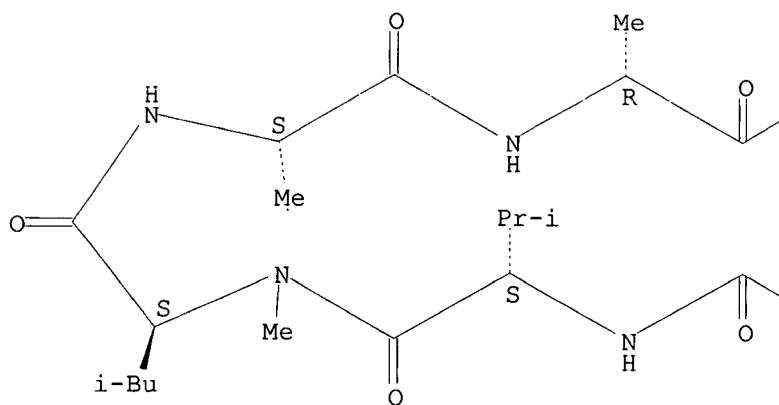
CN Cyclosporin A,

6-[(2S,3R,4R,6E)-3-[[[bis(2-propenyloxy)phosphinyl]oxy]methoxy]-4-methyl-2-(methylamino)-6-octenoic acid]- (9CI) (CA INDEX NAME)

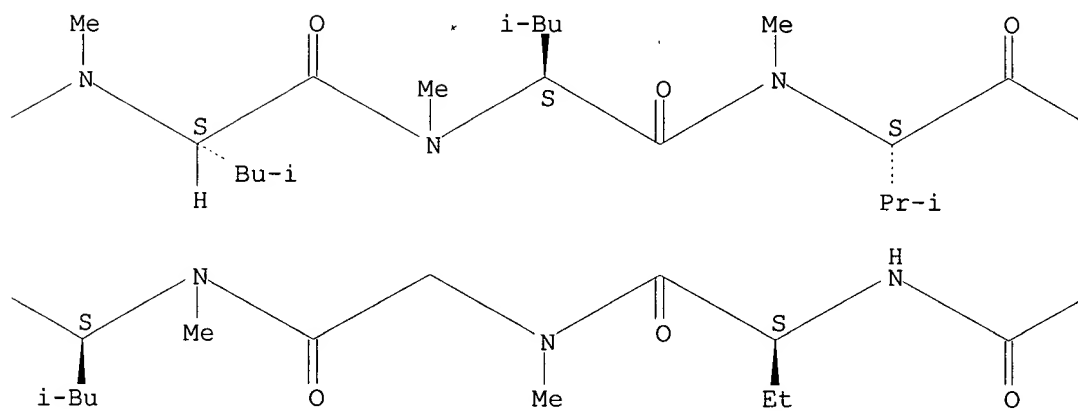
Absolute stereochemistry.

Double bond geometry as shown.

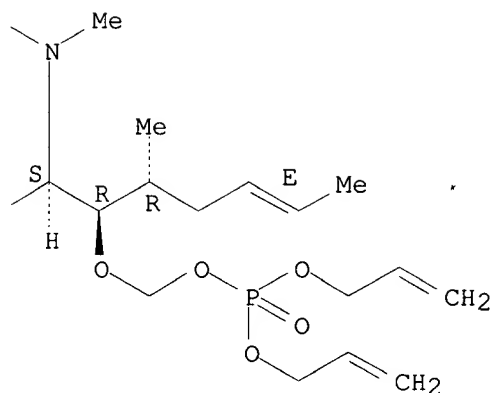
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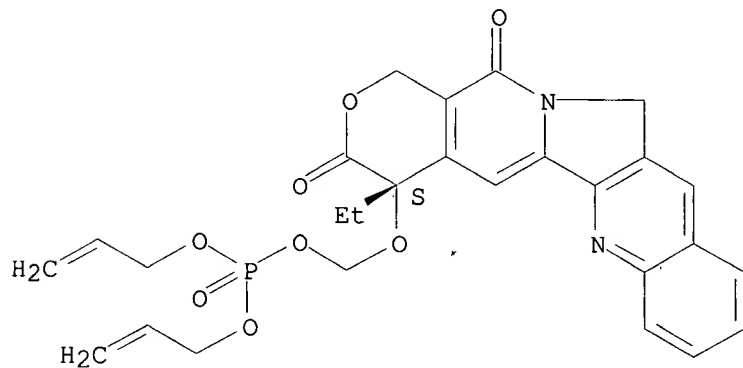
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RN 258516-78-8 HCAPLUS

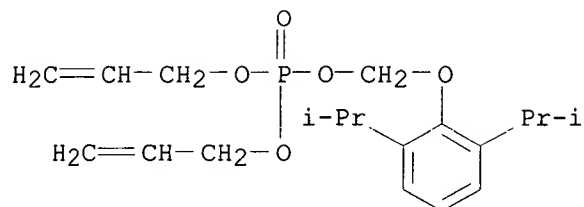
CN Phosphoric acid, [[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl]oxy]methyl di-2-propenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



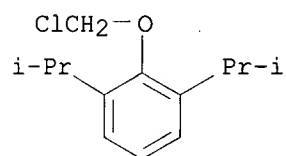
RN 258516-80-2 HCAPLUS

CN Phosphoric acid, [2,6-bis(1-methylethyl)phenoxy]methyl di-2-propenyl ester (9CI) (CA INDEX NAME)



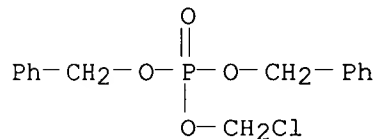
RN 258516-82-4 HCAPLUS

CN Benzene, 2-(chloromethoxy)-1,3-bis(1-methylethyl)- (9CI) (CA INDEX NAME)



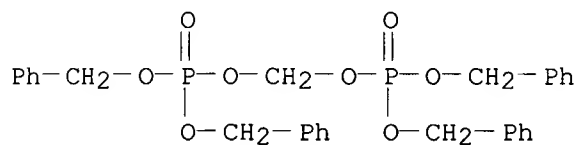
RN 258516-84-6 HCAPLUS

CN Phosphoric acid, chloromethyl bis(phenylmethyl) ester (9CI) (CA INDEX NAME)



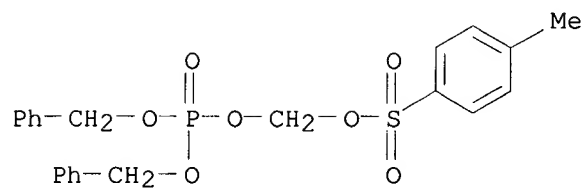
RN 258516-85-7 HCAPLUS

CN Phosphoric acid, methylene tetrakis(phenylmethyl) ester (9CI) (CA INDEX NAME)



RN 258517-06-5 HCAPLUS

CN Phosphoric acid, [[(4-methylphenyl)sulfonyl]oxy]methyl bis(phenylmethyl) ester (9CI) (CA INDEX NAME)



RE.CNT 5

RE

- (1) Bristol-Myers Squibb Co; EP 0604910 A 1994
- (2) Bristol-Myers Squibb Co; EP 0639577 A 1995
- (3) Bristol-Myers Squibb Co; EP 0747385 A 1996
- (4) Golik, J; BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1996, V6(15), P1837
HCAPLUS
- (5) Safadi, M; PHARMACEUTICAL RESEARCH 1993, V10(9), P1350 HCAPLUS